A response to the PTO 498 is attached herewith.

Claims 59, 62, 63, 65, 66 and 76 have been objected to for informalities. Claim 66 has been cancelled and claims 59, 62, 63, 65 and 76 have been amended to correct these informalities. Withdrawal of the objection is requested.

Claims 59-63, 65-66 and 72-76 have been rejected under 35 U.S.C. 112, first paragraph. The Office Action states that the specification is enabling for methods involving the administration of an alkaloid or radiation in combination with "directly administering" to a tumor of a mammal a target cell-specific adenovirus vector, but is not enabled for the full scope of the claimed invention.

Applications respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112. The claims have been amended to recite that the treatment is directed to a mammal.

The Office Action states that the methods of the present invention lie in the field of gene therapy. In the methods of the present invention, an adenovirus is delivered to a patient. The adenovirus has been constructed so as to replicate only in selected cells, because adenoviral genes required for replication of the virus are under the control of a cell-specific transcriptional regulatory element. When the virus replicates, it causes lysis of the host cells. There is no DNA therapy. Rather, the present invention involves a replicating biological agent.

The Office Action has questioned the targeting of "delivery systems" (see office action, page 7, second paragraph). However, the present invention does not rely on targeting of the vector in the sense that the adenovirus is only delivered to specific cells. Rather, the present invention relies on selective replication, such that the adenovirus is ineffective in replicating in any but the cells of interest. Concerns such as the protection of the adenovirus from degradation, sequestration or immune attack are answered by the data provided in the examples.

Applicants respectfully draw the Examiner's attention to Example 1, page 103 ff, which states that the prostate specific adenovirus "CV787 alone can, in a single intratumoral dose ($lx10^8$ particles per $mm^3$ of tumor) or a single intravenous dose ($1x10^{11}$ particles per animal) eliminate established tumors within 6 weeks in nude mouse xenografts." In testing the presently claimed combination therapies (see page 110, lines 1-8) the adenovirus was administered by i.v. injection. Although the Office Action states that the disclosure does not reasonably correlate to a method of cancer gene therapy using intravenous administration of the adenoviral vector, Applicants respectfully submit that

systemic administration, as exemplified by intravenous administration, is well supported by the specification and examples.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention meets the requirements of 35 U.S.C. 112, first paragraph. Withdrawal of the rejection is requested.

Claims 59-63, 65-66 and 72-76 have been rejected under 35 U.S.C. 112, second paragraph. The Office Action states that the claims fail to recite the target of the adenovirus and how it suppresses tumor growth. Applicants respectfully submit that the target of the adenovirus is defined by the cell-specific transcriptional regulatory element, as recited in the claims. A prostate specific TRE replicates in cells of the prostate, and is therefore selectively replicated (targeted) to prostate cancers. The claims have been amended to recite that the adenovirus is replication competent, thereby clarifying the role of adenovirus replication and host cell cytolysis in the methods of the invention.

The claims have been amended such that the claim completes the preamble, by reciting the suppression of tumor growth.

The phrase "less than that known in the art" has been amended to recite that the dose of antineoplastic agent or radiation delivered in the present methods is less than the effective dose for suppressing tumor growth when administered alone. Applicants respectfully submit that doses of the recited antineoplastic agents currently in clinical use are known or can be readily determined. In the present methods, the antineoplastic agent is provided at a dose that is lower than the current clinical dose for that particular antineoplastic agent together with a replication competent target cell-specific adenovirus, the combination of which is effective in suppressing tumor growth.

In view of the above amendments and remarks, Applicants respectfully submit that the present claims meet the requirements of 35 U.S.C. 112, second paragraph. Withdrawal of the rejection is requested.

Claims 59, 61, 66 and 72-73 have been rejected under 35 U.S.C. 103 as unpatentable in view of Henderson *et al.*, U.S. 5,871,726; taken with Kirn et al. (WO99/59604). Henderson teaches replication competent, cell-specific adenovirus vectors. Kirn teaches combination of cisplatin and adenoviral vector. Applicants respectfully submit that the present claims are not taught or suggested by the cited combination of references.

Kirn teaches combination therapy based on wild-type adenovirus (page 5, line 4) or adenoviruses that lack a viral protein that inactivates p53 together with cisplatin. Kirn does not

teach an adenovirus having a gene essential for replication under the control of a cell-specific transcriptional regulatory element, wherein the target cell-specific adenovirus results in virus replication-dependent cytolysis in combination with paclitaxel, docetaxel, doxorubicin or etoposide. The current claims do not recite cisplatin.

One of skill in the art could not have predicted the effect of combined therapy utilizing the adenovirus of the present invention, together with paclitaxel, docetaxel, doxorubicin or etoposide based on the disclosure of Kirn.

Henderson *et al.* teaches a cell-specific, replication competent adenovirus, but does not teach the benefits of a combination immunotherapy. One could not have predicted the effectiveness of the combined therapy based on the disclosure of the adenovirus, because the adenovirus works by virus replication-dependent cytolysis. Henderson *et al.* does not compensate for the lack of disclosure of the effect of combined therapy utilizing an adenovirus of the present invention, together with paclitaxel, docetaxel, doxorubicin or etoposide. Hence, taken together the cited references do not teach or suggest the present invention. It is only in view of the data provided by the present application that one could reasonably have predicted the efficacy of the claimed invention.

Applicants respectfully submit that the present invention is not made obvious by the cited combination of references. Withdrawal of the rejection is requested.

Claims 59, 60, 61, 62, 63, 65, 66 and 72-73 have rejected as unpatentable over Henderson taken with Gurnani. Gurnani teaches that p53 adenovirus combined with cisplatin, doxorubicin, paclitaxel, methotrexate or etoposide inhibited cell proliferation more effectively than chemotherapy alone. Applicants respectfully submit that the presently claimed invention is not made obvious by the cited combination of references. The deficiency of Henderson as a reference for this purpose is discussed above.

Gurnani *et al.* teach the use of replication deficient adenovirus as a means of gene therapy. The adenovirus does not replicate and cause cytolysis of the host cell; it is merely a means of delivering the gene of interest – a p53 tumor suppressor gene under the control of a cytomegalovirus promoter.

The underlying mechanisms of action are completely different between the methods taught by Gurnani and the presently claimed invention. One of skill in the art would not be able to predict the effect of a replication competent cytolytic adenovirus, based on extrapolation from the prior art adenoviral vector, which is not replication competent, not cell-specific and not cytolytic. The effectiveness of the presently claimed combination could not have been predicted by the results of the data obtained with an unrelated adenoviral entity.

Applicants respectfully submit that the present invention is not made obvious by the cited combination of references. Withdrawal of the rejection is requested.

Claims 59, 73 and 74 are rejected as above, and further in view of Duque *et al.* Duque *et al* teach that 19 kda and 55 kda E1B deficient adenovirus induced cytopathic effect higher than for wild type adenovirus.

Applicants respectfully submit that Duque *et al.* does not remedy the deficiencies of the primary references. One of skill in the art would not have been able to predict that the adenovirus as set forth in the present claims would effectively replicate and cause cytolysis of tumor cells when the tumor cells are also exposed to anti-neoplastic drugs, because the adenovirus activity relies on selective replication in the targeted host cells. The deletion of the 19 kDA region does not alter the requirement of a host cell for adenovirus replication. Duque *et al.* fails to make up for the deficiency in the primary references and does not teach or suggest that a combination therapy as set forth in the claims would be effective, or could have a synergistic effect.

Applicants respectfully submit that the present invention is not made obvious by the cited combination of references. Withdrawal of the rejection is requested.

Claim 75 has been rejected as unpatentable over Henderson in view of Chiang. Chiang teaches radiation therapy combined with gene therapy, where cells are transfected with an adenoviral vector comprising a DNA sequence encoding wild-type p53. Chiang teaches the use of replication deficient adenovirus as a means of gene therapy. The adenovirus does not replicate and cause cytolysis of the host cell; it is merely a means of delivering the gene of interest – a p53 tumor suppressor gene. The underlying mechanisms of action are completely different between the methods taught by Chiang and the presently claimed invention, which does not rely on delivery of a tumor suppressor gene to a targeted cell.

Radiation deposits energy that injures or destroys cells in the area being treated. Radiation injury to cells is nonspecific, with complex effects on DNA. Frequently irradiated cells undergo apoptosis. One of skill in the art could not have predicted that adenovirus would be able to successfully replicate in cells that are undergoing radiation therapy, as the cellular metabolism is severely disrupted under these conditions. Because gene therapy does not rely on replication of the adenovirus within the cell, the success of the presently claimed invention could not have been predicted based on the prior art. Withdrawal of the rejection is requested.

## CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-017.

Respectfully submitted,

Date: January 23, 2003

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Cancel claims 64, 65 and 67-71.

59. (amended) A method for suppressing tumor growth in [an individual] a mammal comprising:

administering a replication competent, target cell-specific adenovirus [vector], said [vector] adenovirus comprising an adenoviral early gene essential for replication under transcriptional control of a target cell-specific transcriptional regulatory element (TRE), selected from the group consisting of a prostate-specific antigen (PSA)-TRE, an α-fetoprotein (AFP)-TRE and a human uroplakin II (UPII)-TRE wherein said target cell-specific adenovirus results in virus replication-dependent cytolysis; and

at least one antineoplastic agent selected from the group consisting of paclitaxel, docetaxel, doxorubicin and etoposide, [wherein the amount of antineoplastic agent administered is] at a dose less than [that known in the art to be] the effective dose for suppressing tumor growth when administered alone,

wherein said tumor growth is suppressed.

62. (amended) A method for suppressing tumor growth in [an individual] a mammal comprising:

administering a replication competent, target cell-specific adenovirus [vector], said [vector] adenovirus comprising an adenoviral gene essential for replication under transcriptional control of a prostate-specific antigen (PSA)-TRE wherein said target cell-specific adenovirus results in virus replication-dependent cytolysis; and

at least one antineoplastic agent selected from the group consisting of etoposide, [estramustin and 5-fluorouracil (5-FU)], paclitaxel, docetaxel and doxorubicin, [wherein the amount of antineoplastic agent administered is] at a dose less than [that known in the art to be] the effective dose for suppressing tumor growth when administered alone,

wherein said tumor growth is suppressed.

75. A method for suppressing tumor growth in [an individual] a mammal comprising:

administering a replication competent, target cell-specific adenovirus [vector], said [vector] adenovirus comprising an adenoviral gene essential for replication under transcriptional control of a target cell-specific transcriptional regulatory element (TRE), selected from the group consisting of a

prostate-specific antigen (PSA)-TRE, an α-fetoprotein (AFP)-TRE and a human uroplakin II (UPII)-TRE wherein said target cell-specific adenovirus results in virus replication-dependent cytolysis; and

[administering] an effective amount of an appropriate course of external radiation therapy to said mammal [wherein the amount of radiation administered is] at a dose less than [that known in the art to be] the effective dose for suppressing tumor growth when administered alone,

wherein said tumor growth is suppressed.

76. (amended) The method of claim [77] 75, wherein said TRE is a prostate-specific antigen (PSA)-TRE.

Add the following new claims:

77. (new) A method for suppressing tumor growth in a mammal comprising:

administering a synergistic combination of

a replication competent, target cell-specific adenovirus, said adenovirus comprising an adenoviral gene essential for replication under transcriptional control of a prostate-specific antigen (PSA)-TRE wherein said target cell-specific adenovirus results in virus replication-dependent cytolysis; and

at least one antineoplastic agent selected from the group consisting of etoposide, estramustin, paclitaxel, docetaxel and doxorubicin, in a combined dosage effective to substantially reduce the numbers of said targeted solid tumor cell population,

wherein said tumor growth is suppressed.

78. (new) The method according to Claim 59, wherein said adenovirus is administered by site-specific injection.

79. (new) The method according to Claim 59, wherein said adenovirus is administered by intravenous injection.